Paper No. 19

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JAN VANDENBERK, LUDO E.J. KENNIS
and ALBERTUS H.M.T. VAN HEERTUM

Appeal No. 1997-3186
Application 08/362,529

ON BRIEF

Before KIMLIN, GARRIS and WARREN, *Administrative Patent Judges*.

WARREN, *Administrative Patent Judge*.

Decision on Appeal

This is an appeal under 35 U.S.C. § 134 from the decision of the examiner finally rejecting claims 1, 2, 6 and 11 through 29. Subsequent to the final rejection, appellants canceled claims 26 through 29 and added claims 30 through 33,[1,2] of which the examiner has rejected claims 30 and 33 and allowed claims 31 and 32. Accordingly, claims 1, 2, 6, 11 through 25, 30 and 33 are before us in

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[1] Amendment of April 24, 1996 (Paper No. 9) which was entered by the examiner in the advisory action of May 16, 1996 (Paper No. 10).

[2] The examiner observes error in the copy of claim 2 in the appendix to the brief (answer, page 3). We leave the matter of the appropriate terminology for a fluorobenzyl group (*id*.) to the examiner for resolution subsequent to this appeal as resolution here is not necessary to our decision.

this appeal. Claim 1 is illustrative of the claims on appeal, a copy of which taken from the appendix to appellants' brief is appended to this decision.

The appealed claims as represented by claim 1[3] are drawn to a compound having a structural formula as defined in the claim. Appealed claims 30 and 33 are respectively drawn to methods of inhibiting neuronal serotonin reuptake in warm blooded animals and of inhibiting the affinity of serotonin to $5HT_{1A}$ receptors in warm blooded animals, wherein a therapeutically effective amount of a claimed compound is administered to the warm blooded animals. The examiner has allowed claims 31 and 32 which are respectively drawn to methods of antagonizing the action of reserpine in warm blooded animals and of antagonizing the action of dopamine in warm blooded animals, wherein a therapeutically effective amount of a claimed compound is administered to the warm blooded animals.

The references relied on by the examiner are:

Kennis et al. (Kennis '451)	4,443,451	Apr. 17, 1984
Kennis et al. (Kennis '663)	4,804,663	Feb. 14, 1989
Kennis et al. (Kennis '255)[4] (published Eur. Pat. Application)	0 378 255	Jul. 7, 1990

The examiner has rejected appealed claims 1, 2, 6, 11 through 25, 30 and 33 under 35 U.S.C. § 103 as being unpatentable over Kennis '451 and Kennis '663, both independently in view of Kennis '255. We affirm.

Rather than reiterate the respective positions advanced by the examiner and appellants, we refer to the examiner's answer[5] and to appellants' brief for a complete exposition thereof.

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[3] Appellants state in their brief (page 4) that the appealed claims "stand or fall together." Thus, we decide this appeal based on appealed claim 1. 37 CFR § 1.192(c)(7) (1995).

[4] Appellants observe that "the U.S. equivalent of [Kennis '255] is U.S. Patent No. 5,140,029" ('029 patent) (brief, page 4).

[5] The examiner refers to the Office action of June 27, 1995 (Paper No. 5; pages 4-5) for the statement of the ground of rejection (answer, page 4), and to the Office action of May 16, 1996 (Paper No. 10; pages 2-4) for his response to the arguments presented by appellants at pages 4-8 of the brief (answer, page 4). The referral to more than one prior Office action in an examiner's answer is inappropriate, but in this instance, because the issues are straightforward and developed, we will not remand this application for consolidation. *See* Manual of Patent Examining Procedure § 1208 (6th ed., Rev. 2, July 1996, 1200-14; 7th ed., Rev. 1, Feb. 2000, 1200-14).

Opinion

We have carefully reviewed the record on this appeal and based thereon find ourselves in agreement with the supported position advanced by the examiner in the answer that, *prima facie*, one of ordinary skill in this art would have found in the combined teachings of the three Kennis references, the suggestion to substitute a bicyclic 3- benzofuranyl or a bicyclic 3-benzothienyl group[6] for the bicyclic 3-indole group of Kennis '451,[7] or for the bicyclic 3-benzisoxazole or the bicyclic 3-benzisothiazole group of Kennis '663,[8] in the 4 - position of the piperidinyl group of the compounds of these two references as suggested by the use of these same groups in the same position in the closely structurally related compounds disclosed in Kennis '255,[9] in the reasonable expectation of obtaining compounds which have similar properties with respect to the utility as serotonin antagonists with various therapeutic uses when administered to warm blooded animals.[10] Accordingly, *prima facie*, one of ordinary skill in this art following the teaching of the combined references would have reasonably arrived at compounds which satisfy each of the limitations of the claimed compounds encompassed by claim 1. *See In re Payne*, 606 F.2d 303, 315, 203 USPQ 245, 254-55 (CCPA 1979) ("An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties."); *see also In re Jones*, 958 F.2d 347, 349-51, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992) ("Conspicuously missing from this record is any *evidence*, other than the PTO's speculation (if it be called evidence) that one of ordinary skill in the herbicidal art would have been motivated to make the

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[6] See the definition of formula member "X" in appealed claim 1; and the definition of formula member "B is O, S" in the structure "(a-3)" in Kennis '255 (e.g., page 3, lines 40-44 and 49).

[7] See the structure "(b)" in the definition of formula member "Q" in Kennis '451 (e.g., col. 1, lines 67-68, and col. 2, lines 23-32); and the definition of formula member "B" as "NR^8", wherein formula member "R^8 is hydrogen," in the structure "(a-3)" in Kennis '255 (e.g., page 3, lines 40-44 and 49).

[8] See formula member "X is O or S" in Kennis '663 (e.g., col. 1, line 39); and the definition of formula member "B is O, S" in the structure "(a-2)" in Kennis '255 (e.g., page 3, lines 33-37 and 49).

[9] Kennis '255 teaches that "X is CH in case R^1 is a radical of the formula (a-1), (a-2) or (a-3)" which is the same piperidinyl group structure in the same position as in the claimed compounds and the cited compounds of Kennis '451 and '663.

[10] See Kennis '451 (e.g., col. 11, line 23, and col. 14, line 51, to col. 15, line 22), Kennis '663 (e.g., col.. 9, lines 17-24), and Kennis '255 (e.g., page 14, lines 11-22).

modifications of the prior art salts necessary to arrive at the claimed . . . salt."); *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(*in banc*) ("This court . . . reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness, and that the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case."); *In re Grabiak*, 769 F.2d 729, 731-32, 226 USPQ 870, 872 (Fed. Cir. 1985) ("[W]e have concluded that generalizations should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other. . . . [I]n the case before us there must be adequate support in the prior art for the ester/thioester change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant.")

Accordingly, since a *prima facie* case of obviousness has been established based on the applied prior art with respect to appealed claim 1 by the examiner, we have again evaluated all of the evidence of obviousness and nonobviousness based on the record as a whole, giving due consideration to the weight of appellants' arguments in the brief and the declaration of Dr. Meert in light thereof.[11] *See generally, In re Johnson*, 747 F.2d 1456, 1460, 223 USPQ 1260, 1263 (Fed. Cir. 1984).

Appellants present two issues in rebuttal (brief, pages 4-5). First, appellants submit that the examiner is in error in finding that the claimed compounds are structurally obvious. Appellants point to "representative formulas" of the references and identify the right hand side containing the "ALK" linkage as the "head" moiety and the left hand side as the "tail" moiety, and allege that the claimed compounds can only "be obtained by substituting" the entire "head" moiety of the compounds of Kennis '255[12] which requires severing the compounds of the Kennis references and reconstructing them by adding the "tail" moiety of one to the "head" moiety of another, which might be "obvious to try" (brief, pages 5-7). Appellants further point to the "tail" moiety of the compounds of Kennis '255, characterizing the same as involving "amino substitution at the 2-position of the pyrimidinone moiety" and noting that the compounds of both Kennis '451 and '663 "have sulfur substitution at this position," in contending that

[11] The declaration was filed April 24, 1996 (Paper No. 9).

[12] With respect to appellants' arguments based on the "029 patent (brief, e.g., page 6), *see above* note 4.

"any equivalency taught by [Kennis '255 with respect to the "head" moiety] is only applicable when the 2-amino substitution is present on the pyrimidinone ["tail"] moiety" (brief, pages 8-9).

The examiner contends with respect to the "obvious to try" standard as explained in *In re O'Farrell*, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), that Kennis '255 provides "more than general guidance" with respect to the substitution in the "4-piperidinyl position" since this reference "gives an indication and direction that the replacement of the bicyclic group" in this position of the other Kennis compounds "is likely to be successful since they are equivalent in the art" (*see above* note 5; Paper No. 10, pages 2-3). The examiner further contends that the compounds of the Kennis references are "sufficiently close in structure to be considered together" by one of ordinary skill in the art such that "all of the references together" would have suggested that the substituents in the 4-position of the piperidinyl group of Kennis '255 are equivalent and can be used in place of those in the same position of the compounds of Kennis '451 and '663, "thus fairly suggesting the instant compounds with the reasonable expectation that similar pharmacological activities would result" (answer, page 5). In this respect, the examiner points out that "[a]ll [of the Kennis compounds] are directed to bicyclic pyrimidinone-alkyl-piperidine compounds having a bicyclic substituent at the 4-position of the piperidine group" and "are directed to the same kind of pharmacological activity and therapeutic uses, i.e., as serotonin antagonists and as psychotic agents, anxiolytics and antiagressive compounds" (*id*.). The examiner further points out that the compounds of Kennis '451 differ solely in the presence of a "ring nitrogen in the [bicyclic] indole ring (b) at Col. 2" rather than "an oxygen or sulfur atom" in the same position and Kennis '255 "teaches this atom equivalency at this position" (answer, page 6; *see above* notes 6 and 7).

We have carefully considered the evidence in the combined teachings of the applied references in light of the opposing arguments and find ourselves in agreement with the examiner that the combined teachings of the three Kennis references must be considered for the teachings or inferences that would have been drawn therefrom by one of ordinary skill in this art. *See In re Fritch*, 972 F.2d 1260, 1264-65, 23 USPQ2d 1780, 1782-83 (Fed. Cir. 1992); *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981) ("[T]he test [for obviousness] is what the combined teachings of the references would have suggested to those of ordinary skill in the art."). We find that one of ordinary skill in this art

would have found with respect to the bicyclic pyrimidinone "tail" moiety, that the compounds of Kennis '451 have and the compounds of Kennis '663 can have, *inter alia*, a sulfur atom in the 2-position of the bicyclic pyrimidinone "tail" moiety; that the "head" moiety of Kennis '451 can contain a bicyclic indole in the 4-position of the piperidinyl group which falls within the structure "(a-3)," wherein "B" is "NR^8", in the same position in Kennis '255; and that the "head" moiety of Kennis '663 contains a bicyclic structure in the 4-position of the piperidinyl group that fall within the bicyclic structure "(a-2)," wherein "B is O, S", in the same position in Kennis '255. This person would also have recognized that the "head" moiety of Kennis '451 can also contain in the 4-position of the piperidinyl group, a group of the formula "-X-Ar," wherein "X" can be "-C(=O)-" and "Ar" can be "phenyl" (col. 1, line 67, to col. 2, line 6, col. 2, line 37), that is, a benzoyl group, which falls within the structure "(a-1)" in the same position in Kennis '255. Thus, one of ordinary skill in this art would have recognized that the compounds of Kennis '451 and '663 which have the same and similar bicyclic pyrimidinone "tail" moieties, contain "head" moieties having substituents in the 4-position of the piperidinyl group that fall within the three groups identified by the structures "(a-1)," "(a-2)," and "(a-3)" which are taught in Kennis '255 to provide compounds with the same and similar pharmacological properties (e.g., page 14, lines 11-15), which pharmacological properties are also the same as or similar to the pharmacological properties taught in Kennis '451 and '663 (*see above* note 10).

Therefore, based on this evidence, we are of the opinion that one of ordinary skill in the art would have had the reasonable expectation from the combined teachings of the applied references that the modification of the compounds of Kennis '451 and '663 by using "head" moieties containing substituents falling within the formulae "(a-1)," "(a-2)," and "(a-3)" taught in Kennis '255 in the 4-position of the piperidinyl group, including a bicyclic 3- benzofuranyl or a bicyclic 3-benzothienyl group falling within the formula "(a-3)," would result in compounds having the same or similar pharmacological properties as taught in the references.

In arriving at our conclusion, we are not unmindful of the presence of the ring sulfur attached to the 2-position of the bicyclic pyrimidinone "tail" moiety of the compounds of Kennis '451 and '663 and the presence of a ring nitrogen in the same position in the "tail" moiety of the compounds of Kennis '255, as pointed out by appellants. However, appellants have not established on this record that this difference

would have led one of ordinary skill in this art away from using substituents in the 4-position of the piperidinyl group of the "head" moiety that are similar to those in the same position in the Kennis '451 and '663 compounds as shown by Kennis '255, which suggestion this person would reasonably have found in the combined teachings of the references, based on consideration of chemical structure and utility. In this respect, we observe that the bicyclic pyrimidinone "tail" moiety basically contains two ring nitrogens in the pyrimidinone ring, wherein the ring nitrogen in the 3-position of the pyrimidinone ring is common to both rings of the bicyclic moiety; and that while the bicyclic pyrimidinone "tail" moiety of Kennis '255 contains a third ring nitrogen attached to the 2-position of the pyrimidinone ring, the bicyclic pyrimidinone "tail" moiety of Kennis '451 can also contain a third ring nitrogen when the bivalent radical "A" is "-C(R^6)=N-," wherein this ring nitrogen is attached to the 3-position of the pyrimidinone ring (col. 1, lines 53 and 57). Thus, in view of the similar nitrogen content between the compounds of the references, the basis for appellants' contention is not readily apparent from the record.[13]

The second issue presented by appellants is that the examiner is in error in finding "that the newly discovered property (embodied in the reserpine tremor test) does not impart patentability to the compounds unless comparative testing shows that either the prior art compounds do not exhibit activity in the reserpine tremor test or that the subject compounds are unexpectedly superior" (brief, pages 4-5). Appellants submit "that the teachings of the prior art would not have predicted the subject claimed compounds performance in the reserpine tremor test" relying on the conclusion expressed by Dr. Meert in his declaration "that results in the ATN test and the 48/80 test . . . cannot be used to predict results in the reserpine tremor test" (brief, page 7). Thus, appellants contend that, in the absence of authority for the examiner's position, it is not necessary to make any further showing "because no prima facie case of obviousness with respect to performance in the reserpine tremor test has been made out" (*id*., page 8). We observe that appellants do not contend that the methods of inhibiting neuronal serotonin reuptake in warm blooded animals and of inhibiting the affinity of serotonin to $5HT_{1A}$ receptors in warm blooded animals, wherein a therapeutically effective amount of a claimed compound is administered to the warm

[13] *Cf. In re Baxter Travenol Labs.*, 952 F.2d 388, 392, 21 USPQ2d 1281, 1285 (Fed. Cir. 1991) ("It is not the function of this court to examine the claims in greater detail than argued by appellant, looking for nonobvious distinctions over the prior art.").

blooded animals, as set forth in appealed claims 30 and 33, would not have been predicted from the combined teachings of the applied references; and that the examiner has allowed claim 31 drawn to methods of antagonizing the action of reserpine in warm blooded animals.[14]

We cannot agree with appellants' position. Either of the evidentiary showings suggested to appellants by the examiner would serve appellants' case for nonobviousness. *See generally, Dillon, supra* (Rebuttal of a *prima facie* case of obviousness by an applicant "can consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have [citations omitted] . . . ."). However, appellants' mere reliance on their discovery of a new property not suggested by the combined teachings of the prior art does not amount to a showing of an actual difference in properties that would rebut the expectation of similar properties between the claimed compounds and the compounds of the references based on the common properties reasonably expected to be shared by these compounds from the combined teachings of the references. *In re Hoch*, 428 F.2d 1341, 1343-44, 166 USPQ 406, 409 (CCPA 1970) (no evidence was introduced into the record); *cf. In re Wilder*, 563 F.2d 457, 460-61, 195 USPQ 426, 429-30 (CCPA 1977) (evidence of record established an actual difference between claimed compound and one of two structurally similar prior art compounds for a property disclosed for the claimed compound, but did not establish an actual difference in properties between the claimed compound and the other prior art compound based on this property or a property taught for the prior art compound); *In re Mod*, 408 F.2d 1055, 161 USPQ 281, 283 (CCPA 1969) (evidence of record

[14] The examiner has also allowed claim 32 drawn to methods of antagonizing the action of dopamine in warm blooded animals. The examiner did not set forth in the record any reason why claim 32 was allowed in the Office action of May 16, 1996 (Paper No. 10; page 4), which was not the case for claim 31 ("The Examiner concedes that such a new use is not suggested – as indicated by the allowance of the claim to antagonizing the action of reserpine (claim 31)."). We observe that Kennis '255 discloses that the compounds containing substituents falling within the formulae "(a-1)," "(a-2)," and "(a-3)" in the 4-position of the piperidinyl group show antagonism against dopamine (page 14, lines 11-12 and 16-17). Accordingly, we suggest that the examiner reconsider the allowance of claim 32 in light of the combined teachings of the references applied to the appealed claims, and if on reconsideration the current status of this claim is maintained, provide reasons for allowance thereof on the record.

established no actual difference in properties between claimed and prior art compounds based on property disclosed for the claimed compound or on property taught for the prior art compound).

Accordingly, based on our consideration of the totality of the record before us, we have weighed the evidence of obviousness found in the combined teachings of the Kennis references with appellants' countervailing evidence of and argument for nonobviousness and conclude that the claimed invention encompassed by appealed claims 1, 2, 6, 11 through 25, 30 and 33 would have been obvious as a matter of law under 35 U.S.C. § 103.

The examiner's decision is affirmed.

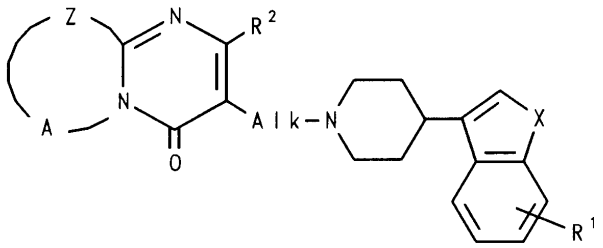
No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

EDWARD C. KIMLIN	)	
Administrative Patent Judge	)	
	)	
	)	
	)	
BRADLEY R. GARRIS	)	BOARD OF PATENT
Administrative Patent Judge	)	APPEALS AND
	)	INTERFERENCES
	)	
	)	
CHARLES F. WARREN	)	
Administrative Patent Judge	)	

APPENDIX

1. A compound having the formula:



(I),

a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, wherein:

X is oxygen or sulfur;

R^1 is hydrogen or halo;

R^2 is hydrogen, C_{1-4}alkyl, phenylmethyl or halophenylmethyl;

Alk is C_{1-4}alkanediyl;

-Z-A- is a bivalent radical selected from the group consisting of $-S-CH_2-CH_2-$, $-S-CH_2-CH_2-CH_2-$, $-S-CH=CH-$, $-CH=CH-CH=CH-$, $-C(=CHR^3)-CH_2-CH_2-CH_2-$, $-CH=CH-O-$, $-CHR^4-CH_2-CH_2-$, $-CHR^4-CH_2-CH_2-CH_2-$, and $-CHR^4-CH_2-CH_2-CH_2-CH_2-$;

wherein in said bivalent radicals:

one hydrogen may be replaced by C_{1-4}alkyl;

R^3 is phenyl or halophenyl; and

each R^4 independently represents hydrogen, hydroxy, phenylmethyl or halophenylmethyl.

Audley A. Ciamporcero
One Johnson & Johnson Plaza

New Brunswick, NJ 08933-7003